MINUTES

HUMAN SUBJECTS RESEARCH ADVISORY COMMITTEE
Friday, January 19, 2007
CRC Medical Board Room
3:00 p.m.

Present

Dr. Michael Gottesman, Chair
Dr. Howard Austin, NIDDK/NIAMS
Dr. Fabio Candotti, NHGRI
Dr. Robert Conley, NIDA
Ms. Lisa Coronado, RSC
Dr. John Gallin, CRC
Dr. Christine Grady, CRC/DCB
Dr. Maureen Hatch, NCI SS
Dr. Rohan Hazra, NCI
Dr. Marian Johnson-Thompson, NIEHS
Dr. Barbara Karp, NINDS/NIDCD/NIA/NIMH
Dr. Mitchell Max, NIDCR
Ms. Ann McNemar, for Dr. Grave, NICHD
Dr. Susan Olivo-Marsten, FELCOM Representative
Dr. Koneti Rao, NIAID
Dr. Robert Shamburek, NHLBI
Mr. Craig Wladyka, Protocol Administration Representative
Dr. Alison Wichman, Acting Exec. Sec.
Dr. Richard Wyatt, OIR

Absent

Dr. Gilman Grave, NICHD

Guests

Dr. Lura Abbott, OHSR
Ms. Elaine Ayres, CRC
Ms. Katya Bratslavsky, NCI
Ms. Melissa Bryant, NHLBI
Ms. Doreen Chaitt, NIAID
Mr. Brian Chamberlain, CC/DCRT
Ms. Theresa Doged, CRC, OPS
Ms. Marjorie Gillespie, NINDS
Ms. Anne Gupman, NIDA
Ms. Mary Hall, CC
Ms. Charlotte Holden, OHSR
Ms. Donna Howard, NIMH
Dr. Sara Hull, NHGRI
Ms. Kim Jarema, OPS
Ms. Laura Kimberly, OPS
Dr. Sarah Kindrick, RSC
Dr. Jerry Menikoff, OHSR Director Designate
Ms. Jennifer Morris, NINDS
Mr. Alex Noury, NINDS
Dr. Maryland Pao, NIMH
Dr. Suzanne Pursley-Crotteau, NCI
Ms. Jeanne Radcliffe, NIMH
Dr. Mark Rohrbaugh, OTT
Ms. Cecile Shindell, NIDA
Mrs. Janet Smith, OHSR (Ret.)
Ms. Patricia Sweet, NHLBI
Ms. Darlene Switalski, NIEHS
Ms. Glynnis Vance, NIDDK
Ms. Gretchen Weaver, OGC/E
Ms. Gretchen Wood, NEI
Dr. Jan Yates, NPCS

1. Minutes of the September 8, 2006 meeting. The minutes were approved with technical corrections.

2. Introduction of Dr. Jerry Menikoff. Dr. Gottesman said that it was his pleasure to introduce Dr. Jerry Menikoff, the Director Designate of OHSR. Dr. Menikoff has an M.D. from Washington University and a law degree from Harvard. His medical specialty is ophthalmology and for the past nine years he has been Chair of the IRB at the University of Kansas. Dr. Menikoff said he was very pleased to be at the HSRAC meeting. The IRB Chairs introduced themselves to Dr. Menikoff.

Dr. Gottesman thanked Dr. Alison Wichman, who has served for almost two years as the Acting Director of OHSR, and who is now embarking on a clinical rotation with NINDS. Ms. Charlotte Holden will be the Acting Director, OHSR until Dr. Menikoff's arrival at NIH.

3. Update on Material Transfer Agreements (MTAs). At the recent Congressional hearings about transfer of clinical material outside NIH, the importance of Material Transfer Agreements (MTAs) was highlighted. Dr. Rohrbaugh, Director, Office of Technology Transfer, distributed a document entitled "Material Transfer Guidance", and thanked Dr. Wichman, Ms. Elaine Ayres, and Ms. Charlotte Holden for their input into the document.

The document categorizes the different types of materials that can be transferred from NIH intramural laboratories. It provides guidance on how those materials can be distributed to outside parties, depending on the type of material, the intended use and the type of institution (for-profit or not-for-profit). The document is divided into three parts: (1) Materials NOT obtained directly from human subjects or extracted directly from human samples; (2) Materials or data obtained directly from patients or extracted directly from human samples, and (3) Materials that constitute an invention (patentable subject matter) whether patented or not. The document has columns showing (a) a more detailed description of the materials; (b) delineation of what is the appropriate agreement for various materials (e.g., MTA, modified MTA, UBMTA [Uniform Biological Material Transfer Agreement], Letter of Agreement); (c) a description of who should be the signatory for any agreements (e.g., Laboratory Chief or higher, IC Technology Development Coordinator, Scientific Director, etc.), and (d) additional notes.

In Part 1 of the document, Dr. Karp asked what is her role as IRB Chair in Section D cases, where materials are obtained under NIH IRB-approved protocols but will be used in protocols elsewhere. Is she required to approve the off-site protocol as well, and if so, can approval be expedited? Dr. Gottesman said that the NIH IRB must be comfortable that any outside protocol meets NIH standards. If it does not, the NIH PI may not participate. In cases when materials are used in collaboration with a recipient scientist and an intramural investigator will also be interacting with human subjects or obtaining identifiable information, an NIH-approved protocol is necessary. Dr. Gottesman said Chairs will have to exercise judgment, and reminded them that one of the criteria for collaboration is co-authorship. Collaboration requires NIH IRB approval or an OHSR

exemption. If IRB Chairs are in doubt, they are encouraged to call OHSR to discuss. Dr. Rohrbaugh added that the standard MTA agreement notes that transferred material may not be used for human subjects research.

In Part 2, it was suggested that Clinical Directors be added to the signatory list for materials and data obtained from patients either as part of routine care or under a clinical protocol.

There was discussion about Section B in Part 2, which states that protocols must remain open if samples or data from an NIH clinical protocol can be linked by the NIH investigator to a specific human subject. If data only are transferred, then a data transfer agreement can be obtained from the Institute's Technology Development Coordinator whereby the recipient agrees to comply with human subjects requirements, and the protocol must remain open. Dr. Hazra commented that in NCI, protocols remain open if NCI is a coordinating center for the research, but if it is not a coordinating center, the NCI IRB will allow the protocol to close if there is no further involvement of the NCI PI.

Dr. Wichman questioned to what extent Section A of Part 2 "materials and data obtained from patients as part of routine care" is relevant. Dr. Hazra said that NCI standard of care protocols specify "no research." Dr. Gallin pointed out that if clinical biopsies done as standard of care in association with research protocols are stored, but are not research in themselves, then they would fall under Section A.

Dr. Rohrbaugh was requested to use the term "deidentified" in Section C, instead of "anonymized."

Dr. Rohrbaugh explained Part 3, Section A, "Materials that Constitute an Invention (patentable subject matter) whether patented or not." He said that an invention has been defined as "anything under the sun made by man", and that although nothing human can be invented, patterns of tissue arrays, which overlap with clinical material, have in fact been licensed.

In answer to a question, Dr. Gottesman said that if MTAs exist but are not mentioned in protocols, subjects may need to be re-consented or a waiver of consent could be requested from the IRB.

Dr. Gottesman thought it would be useful to have the Technology Development Coordinators manage a database for their Institutes or for NIH as a whole so that investigators and requestors could download information electronically. NIDDK has already implemented such a system. It is up to the TDCs to make sure that IRBs see all relevant information regarding material transfer relevant to human subjects research.

Dr. Gottesman asked the Chairs to send comments and concerns to Dr. Rohrbaugh.

4. Demonstration of the Consent Writing Module of *Prototype.* Mr. Brian Chamberlain distributed materials to the group and gave a power point presentation illustrating the NIH Consent Authoring Tool.

The current draft incorporates headings that were approved by the CC Informed Consent Working Group (ICWG), chaired by Dr. Wichman. Mr. Chamberlain explained that the purpose of the tool is to create consent documents in a standardized format, based on federal requirements, with headings in the form of questions. Investigators can choose from a database-driven library of standardized language for study drugs, procedures, tests, etc. and can insert the chosen language into the consent document. The standardized language sources can include *ProtoMechanics*, IRB-required text, and investigators' previously-used, IRB-approved language. The Flesch-Kincaid reading level algorithm in this model analyzes the approximate grade level of the text (8th grade) and provides feedback to the author. If there are difficult words in the text, these are flagged and easier-to-read replacements are suggested. The suggested replacements come from *ProtoMechanics* and PlainLanguage.gov glossaries. Sections and headings can be omitted, e.g., for HIV testing when this is not required, but the tool will not allow deletion or alteration of standard required boilerplate language. Some standard language has been incorporated into the body of the document instead of at the end. Dr. Wichman added that some work needs to be done to bring this standard language to a lower-grade reading level approvable by NIH lawyers.

Mr. Chamberlain demonstrated the features of the consent tool while scrolling through a sample consent. It can be downloaded or printed from the web browser. He pointed out that the tool is still in *beta* testing, which means it is functional but improvements are still being made. He requested feedback on its utility and offered to work personally with anyone who would like to test it.

Dr. Gallin said that the Patient Advisory Committee prefers a question-and-answer format for consents, and he reminded the group that consents are for the convenience of the subject, not for the convenience of the investigator or institution. The primary goal is to inform the subject. Dr. Wichman suggested that future options of graphics and/or videos would be even more useful in promoting understanding. She suggested that a worthwhile goal is for consents from all NIH IRBs to look more or less alike and asked if this is a goal HSRAC should be working towards.

Dr. Karp's IRB has used the consent tool and she is concerned that the question-and-answer format is too directive for investigators, who tend to give short answers to the questions. Eventually, her IRB accepted the consent it reviewed with stipulations. Dr. Gottesman agreed that IRBs will have to work to make sure they get the consent information from PIs that they require.

Dr. Rao commented that consent documents are getting longer, and asked whether there could be a consensus about their length. Dr. Wichman was sympathetic, but said that it is hard to be brief when the subject matter is complicated. In any event, almost all consent documents can be shortened with good editing.

Dr. Grady said that comparisons have been made between subjects' preferences for short forms, videos, etc., but accumulated data seem to suggest that nothing replaces a good discussion plus a document. Subjects generally do not understand terms such as "randomization" and "placebo controls." Dr. Wichman agreed that interaction is important as well as continuing education of subjects after consent has been obtained.

Dr. Wichman stressed that it is important to pilot this tool and for IRBs to endorse it.

Dr. Gottesman thanked Mr. Chamberlain for his presentation.

5. Update on the IRP Conflict of Interest Policy. With the agenda, HSRAC members were provided with an updated version of the COI policy reviewed by the Medical Executive Committee in November 2006. Comments from the Clinical Center Division of Ethics in response to a previous MEC meeting were in red. MEC comments in green reflect the minutes of the November 2006 MEC meeting. Dr. Abbott and Ms. Ayers confirmed that this is the most up-to-date version of the COI guidance.

Dr. Wichman asked for comments on the proposed handling of review of Clinical Directors' protocols (page 3). It is expected that most CDs' protocols will be reviewed by other IRBs. Dr. Hazra said that a special arrangement has been made for continued review of Dr. Balis's protocols by the NCI IRB, but this arrangement will not apply to future NCI Clinical Directors. The NHLBI IRB has not yet made a decision on how to handle Dr. Cannon's protocols. Ms. Bryant asked in what circumstances Dr. Cannon's protocols may be reviewed by the NHLBI IRB. Dr. Gottesman responded that the IRB must be comfortable about reviewing his protocols; if they do decide to review them, the IRB must have a majority of non-NHLBI members. Any alternative plan must be approved by Dr. Gottesman and Dr. Gallin. Dr. Rao said that the NIAID continues to review its Clinical Director's protocols when he is an accountable investigator and that the skills of the NIAID IRB are essential to these reviews.

Ms. McNemar pointed out that DSMB members are mentioned in the second bullet on page 3 of the guide, but are not subsequently referred to. This can be corrected in Section VI (page 5), i.e., the heading will read “IRB and DSMB Clearance for COI” and the bullet will read “IRB and DSMB Members.” She also suggested, and it was agreed, that the sentence "in his or her opinion" should be deleted from the bullet on page 3.

Dr. Hatch asked whether a special dispensation could be made to exclude the NCI SS protocols from DEC requirements, since these protocols are mainly observational and rarely involve a potential for conflict of interest. Dr. Gottesman asked Dr. Hatch to continue to follow the conflict of interest rules for now and to check with him again after a year's experience.

Dr. Hazra asked what should be included in the informed consent when the DEC concludes that *de minimus* amounts of stock are held by investigators, i.e., the DEC has decided that the amount of stock held is "below the level that triggers concern" (page 4).

Dr. Hazra said the NCI IRB has decided to describe the process in the consent without going into detail. Dr. Gottesman believes that it is ill-advised for any investigators to own stock when the results of their research could have a direct and predictable effect on the value of that stock.

Dr. Grady said that with the exception of a small and vocal minority, studies have shown that subjects are not interested in details of stock ownership. A general statement in the consent with information on where to get more information is usually sufficient.

Ms. Weaver pointed out that a greater level of conflict of interest review is applied to employee members of IRBs *versus* non-employee IRB members because employees are required to complete financial statements.

Dr. Gottesman commented that the Scientific Directors should review the latest COI guide.

6. Update on the CNS IRB. This agenda item was not discussed.

The meeting adjourned at 5:15 p.m. The next meeting will take place on March 9, 2007.